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Piracetam for reducing the incidence of painful sickle cell disease crises (Review)

Al Hajeri A, Fedorowicz Z

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[Intervention Review]

Piracetam for reducing the incidence of painful sickle cell disease crises

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ABSTRACT

Background

Sickle cell disease is one of the most common genetic disorders. Sickle cell crises in which irregular and dehydrated cells contribute to blocking of blood vessels are characterised by episodes of pain. Treatment is mainly supportive and symptomatic. *In vitro* studies with piracetam indicate that it has the potential for inhibition and a reversal of the process of sickling of erythrocytes. This is an update of a previously published Cochrane review.

Objectives

To assess the effectiveness of piracetam for reducing the incidence of painful sickle cell disease crises.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Haemoglobinopathies Trials Register which comprises of references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.

Last search of the Group's Haemoglobinopathies Trials Register: 21 September 2015.

Selection criteria

Randomised controlled trials comparing orally administered piracetam to placebo or standard care in people, of all ages and both sexes, with sickle cell disease.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. Trial authors were contacted for additional information. Adverse effects data were collected from the trials.

Main results

Three trials involving 169 participants were included in the review. A limited amount of data addressing some of the primary and some of the secondary outcomes were provided, but data were incomplete and based on un-validated assumptions used in the evaluation of outcomes. One trial reported a reduction in the number of pain crises and their severity with active intervention than placebo but presented no data to confirm these results. A second trial presented a monthly global pain score based on the number of sickle cell crises and severity of pain but included no separate data for these primary outcomes. Although there was no significant difference between the piracetam and placebo periods for the number of days of hospitalisation (P = 0.87) in one trial, inconsistencies in the criteria necessary for hospitalisation during sickle crises did not permit accurate conclusions to be drawn. Two of the trials reported participant satisfaction with piracetam but provided no details as to how this satisfaction had been assessed. There were no reports of toxicity or adverse effects with piracetam other than one participant who experienced dizziness.

Authors' conclusions

The small number of included trials and their poor methodological quality provided insufficient reliable evidence to support the routine use of this medication for preventing the incidence of painful sickle cell disease crises.

We will continue to run searches to identify any potentially relevant trials; however, we do not plan to update other sections of the review until new trials are published.

PLAIN LANGUAGE SUMMARY

Piracetam for reducing the incidence of painful sickle cell disease crises

Review question

We reviewed the evidence to assess the effectiveness of piracetam for reducing the incidence of painful sickle cell disease crises. This is an update of a previously published Cochrane review.

Background

Sickle cell disease is one of the most common genetic disorders and affects about 250 million people (5% of the world's population). It is characterised by sickle-shaped red blood cells which may block blood vessels. This can lead to pain and damage to the major organs such as the brain, liver and spleen. Standard care is mainly supportive and in response to symptoms. Pain is controlled with drugs for pain relief and fluids to improve fluid levels. In vitro studies with piracetam have shown that it hinders the bonding of sickle haemoglobin and the bunching together of platelets. It also makes the blood less sticky and red blood cells more flexible.

Search date

The evidence is current to: 21 September 2015.

Key results

The authors of the review identified three trials, two of which had a cross-over design. The quality of the trials was poor. There were wide differences in the people taking part, the drug dose and the outcomes measured. Three trials are included. They provide some weak and unreliable evidence that piracetam prevents painful sickle cell crises. This lack of reliable evidence illustrates some of the doubt and lack of support for the routine use of this treatment for reducing the incidence of painful sickle cell disease crises. The review authors conclude that future research should aim to provide evidence for people to make informed decisions about whether piracetam is of use. Further randomised controlled trials should be well-designed and reported according to the 'Consolidated Standards of Reporting Trials (CONSORT)' statement.

We will continue to run searches to identify any potentially relevant trials; however, we do not plan to update other sections of the review until new trials are published.

BACKGROUND

Prevalence and aetiology

Sickle cell disease is one of the most common genetic disorders, affecting primarily people of African, Mediterranean, Middle Eastern and Indian descent. Approximately 250 million people (5% of the world's population) carry a potentially pathological haemoglobinopathy gene (WHO 2006). In the USA there are approximately 75,000 African-Americans (NIH 2002) and in the UK 10,000 British people living with sickle cell disease (Davies 1997). As a result of under-reporting, genetic diseases are likely to be systematically underestimated in developing countries, but some reliable data are available. In the Middle East, e.g. Bahrain, the burden of disease is quite high; 1% to 2% of all neonates have sickle cell disease, whilst 11% of the total are carriers of the disease (Al-Arrayed 1995). Several of the neighbouring countries have indicated similar levels of sickle cell disease in their populations, but comprehensive and up-to-date information is scanty and often unavailable.

Sickle cell disease occurs when the haemoglobin variant HbS gene is inherited from both parents (HbSS), which is the most prevalent form of the disease (Serjeant 2001) or from one parent in combination with another haemoglobin variant gene such as (HbSC) or sickle-ß-thalassaemia (S-ß-Thal). People with homozygous sickle cell disease (HbSS) have a mutated beta globin gene (bS), which causes the production of abnormal sickle haemoglobin.

The disease is characterised by the presence of distorted sickle-shaped red blood cells in the blood stream. These arise as a result of the polymerisation (a gelling of the molecules) of the abnormal haemoglobin in the red blood cells when they release their combined oxygen. The accompanying red blood cell dehydration then tends to increase the intracellular concentration of the sickle haemoglobin which may in turn lead to further polymerisation. The presence of these dense, irregular and fragile dehydrated cells can contribute to blocking of blood vessels (vaso-occlusion) which can lead to pain episodes also known as crises, and may even cause damage to major organs.

Symptoms

Most manifestations of the disease are attributed to either premature red cell destruction (haemolysis) or obstruction of blood flow (vaso-occlusion). Vaso-occlusive crises can produce pain particularly in muscles, bone and joints. Severe vaso-occlusion leading to splenic infarction may result in an increased vulnerability to severe infections and exceptionally to acute splenic sequestration (Serjeant 1994).

Life-threatening complications will require hospitalisation (Balkaran 1992) and can include acute chest syndrome (Castro 1994), splenic sequestration (Topley 1981) in addition to the more chronic events of later life resulting from renal disease and heart failure. Children are at exceptional risk of cognitive impairment as a result of the neurological changes which can occur with overt and subclinical strokes (Knight 1995).

Pain is one of the most common symptoms in sickle cell disease. Its onset and severity is unpredictable and recurrent acute episodes can occur throughout life and may require pain medication and hospitalisation (Brozovic 1987).

Treatment options

Standard care for sickle cell crises is mainly supportive and symptomatic, utilising analgesics and hydration for pain control, and may include transfusion for anemia. Prophylaxis with daily oral penicillin has been used to reduce the rate of infection and the mortality related to pneumococcal infection (Davies 2004). Antibiotic therapy should be used to treat resulting infections and the administration of oxygen has been said to be useful in helping relieve some of the symptoms of acute chest syndrome (Davies 1997). Attempts at finding a drug to prevent the red cells from sticking to the walls of blood vessels and each other have had limited success and the options for a successful cure are few.

Hydroxyurea, the subject of another Cochrane Review, is known to raise foetal haemoglobin and decrease cellular dehydration. It has been shown to be both effective and safe in severely affected SS adults but also has recognised side effects such as cytopenia (low white cell or platelet count) and occasional nausea (Jones 2001).

Piracetam

Piracetam (2-oxo-l-pyrrolidine acetamide, Nootropyl), a cyclic derivative of gamma-amino butyrate has been used for the treatment of mental function and dyslexia and as it has no known side effects (Vernon 1991) and in view of its anti-sickling effect in vivo (Moriau 1993) has been considered as a possible therapeutic agent for management of sickle cell disease crises. Most of the in vitro studies with piracetam, have shown that it interferes with HbS polymerisation, causes a reduction in blood viscosity, an increase in erythrocyte elasticity, inhibits platelet aggregation (Asakura 1981; Gini 1987) and has the potential for inhibition and a reversal of the process of sickling of erythrocytes (de Araujo 1977).

Several studies on the efficacy of piracetam in sickle cell disease crises have shown conflicting results (Alvim 2005; El-Hazmi 1998); and this systematic review seeks to assess the available evidence.

Thi is an update of a previously published Cochrane review. We will continue to run searches to identify any potentially relevant trials; however, we do not plan to update other sections of the review until new trials are published.

OBJECTIVES

To evaluate the effectiveness of piracetam for reducing the incidence of painful sickle cell disease crises.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

People with sickle cell disease SS, SC, Sß^0, Sß+ (confirmed by electrophoresis and sickle solubility test, with family studies or DNA tests as appropriate) of all ages and both sexes, in any setting.

Types of interventions

Piracetam administered orally compared to placebo or standard care for a period of up to two years.

Types of outcome measures

Primary outcomes

1. Number of painful sickle cell disease crises
2. Pain
   a. intensity (expressed as scores obtained through any validated patient reported outcomes instrument either generic or sickle cell disease specific)
   b. duration
3. The requirement for opiate treatment during hospitalisation, Accident & Emergency Department visits or on discharge to home.
   a. dose
   b. type
   c. frequency

Secondary outcomes

1. Mortality (number of deaths)
2. Number of life-threatening complications of sickle cell disease (e.g. stroke, acute chest syndrome, infection and acute splenic sequestration)
3. Red cell dehydration
   a. proportion of dense cells
   b. mean corpuscular haemoglobin concentration
   c. mean corpuscular volume
4. Number of other sickle-related events (e.g. priapism, leg ulceration)
5. Quality of life (e.g. absence from school, lost time at work, mobility) as assessed by any validated questionnaire either generic or sickle cell disease specific
6. Hospitalisation: as the number of inpatient days.
7. Participant satisfaction with the medication assessed by any appropriate and validated questionnaire (either generic or sickle cell disease specific)

Adverse effects

We noted and reported any clinically diagnosed hypersensitivity or toxicity in addition to any reports of unacceptable adverse events associated with this medication.

There have been some post hoc changes made to this section, please refer to the Published notes section for further information.

Search methods for identification of studies

Electronic searches

We identified relevant trials from the Cochrane Cystic Fibrosis and Genetic Diseases Group's (CFGDG) Haemoglobinopathies Trials Register using the terms: sickle cell AND piracetam.

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (Clinical Trials) (updated each new issue of *The Cochrane Library*), and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Health Research Council Meetings; and the National Sickle Cell Disease Program Annual Meeting.

For full details of all searching activities for the register, please see the relevant section of the Cystic Fibrosis and Genetic Disorders Review Group Module.

Date of the last search of the Group's Haemoglobinopathies Trials Register: 21 September 2015.

Searching other resources

We did not handsearch any specific journals but we examined the reference lists of any potential clinical trials and the review authors' personal databases of trial reports in an attempt to identify any additional studies or those not identified in the searches.

We contacted investigators of included studies by electronic mail to clarify trial details and asked for information about any additional published and unpublished trials.

Although there was no language restriction on included studies we did not find any relevant non-English papers.

Data collection and analysis

Selection of studies

Two authors Amani Al Hajeri (AAH) and Zbys Fedorowicz (ZF) independently assessed the abstracts of studies resulting from the searches. Full copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision were obtained. The full text papers were assessed independently by the two authors and any disagreement on the eligibility of potentially included studies was resolved through discussion and consensus. After assessment by the authors any duplicate publications or remaining studies that did not match the inclusion criteria were excluded from further review and the reasons for their exclusion were noted in the 'Characteristics of excluded studies' table.

Data extraction and management

The authors collected outcomes data using a pre-determined form designed for this purpose. Both (AAH and ZF) sequentially entered extracted data into the Review Manager (RevMan) software and automatically checked for differences (RevMan 2014). Zbys Fedorowicz (ZF) held the master copy. The authors only included data if there was an independently reached consensus, any disagreements were resolved by consulting with a third author (AO).

1. Trial methods
   a. method of allocation
   b. masking of participants and outcomes
   c. exclusion of participants after randomisation and proportion of losses at follow up
2. Participants
   a. country of origin
   b. sample size
   c. age
   d. sex
   e. inclusion and exclusion criteria

3. Intervention
   a. dose
   b. duration and length of time in follow up
4. Control
   a. control or placebo
5. Outcomes
   a. primary and secondary outcomes mentioned in the section of outcome measures

The authors used this information to help them assess heterogeneity and the external validity of the trials.

Ghazi Omar Tadmouri (GOT) and Ahmed Omran (AO) graded the selected studies independently and assessed every trial reporting a randomized clinical trial according to the criterion grading system described in the 'Cochrane Handbook for Systematic Reviews of Interventions 4.2.5' (Higgins 2005). These authors compared the gradings and discussed and resolved any inconsistencies in the interpretation of inclusion criteria and their significance to the selected studies. The following parameters of methodological quality are listed below.

Assessment of risk of bias in included studies

1. Randomisation

The authors graded this criterion as adequate (A), unclear (B), inadequate (C). Adequate (A) included any one of the following methods of randomisation: computer generated or table of random numbers; drawing of lots; coin-toss; shuffling cards or throw of a dice. The authors judged as inadequate (C) methods of randomisation utilising any of the following: case record number; date of birth; or alternate numbers.

2. Concealment of allocation

The authors graded this criterion as adequate (A), unclear (B), inadequate (C). Adequate (A) methods of allocation concealment included either central randomisation or sequentially numbered sealed opaque envelopes. The authors considered this criterion inadequate (C) if there was an open allocation sequence and the participants and trial authors could foresee the upcoming assignment.

3. Blinding (of participants, researchers and outcome assessment)

We assessed blinding using the following criteria (detection and performance bias):

1. blinding of participants (yes/no/unclear);
2. blinding of caregiver (yes/no/unclear);
3. blinding of outcome assessment (yes/no/unclear).

4. Handling of withdrawals and losses

The authors graded this criterion as yes (A), unclear (B) and no (C) according to whether there was a clear description given of the difference between the two groups of losses to follow up (attrition bias).

Unit of analysis issues

We had intended following current practice for the meta-analysis of data from trials using a cross-over design, by utilising the methods suggested by Elbourne (Elbourne 2002) but due to restrictions on the data that were available from the included studies we were not able to (quantitatively) analyse these data within this review.

Dealing with missing data

We have been in contact with the authors of the Alvim trial, but to date have received no further information eligible for inclusion in the review (Alvim 2005).

Assessment of reporting biases

The paucity of included trials also precluded any planned attempts to assess publication bias through the use of a funnel plot. However, there was evidence from the retrieved results of the electronic searches, that there had been multiple publications of two of the included trials (Alvim 2005; El-Hazmi 1998).

Data synthesis

Advice was obtained from the Cochrane Cystic Fibrosis and Genetic Disorders Group regarding data synthesis. Any data which had been reported in the included trials and was relevant to the primary and secondary outcomes of this review were to be analysed by two authors (AAH and GOT) using RevMan 5 and reported according to Cochrane criteria (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

Clinical homogeneity of the included trials was assessed by examining the characteristics of the studies i.e.: the similarity between the types of participants, the interventions and the outcomes. However, because of intra-trial heterogeneity in terms of: the characteristics of the participants; the dose and mode of administration of the intervention; and the outcomes reported, pooling of the results and meta-analysis of the extracted data was not feasible and therefore this review only provides a descriptive summary of results of the individual trials.

Sensitivity analysis

As there were insufficient included studies it was not possible to conduct any sensitivity analyses in this systematic review.

RESULTS

Description of studies

Results of the search

The electronic searches retrieved five citations to two trials (Alvim 2005; El-Hazmi 1998); three of these to the El-Hazimi trial and two to the Alvim trial (Alvim 2005; El-Hazmi 1998). The abstracts of these references were assessed independently by two of the authors (AAH/ZF). Scrutinisation of the bibliographical references of these papers identified an additional six references for which we obtained full text copies (De Araujo 1977; De Melo 1976; Franklin 1980; Gini 1987; Mikati 1983; Sonnet 1985). Therefore, a total of eight potential studies were subjected to further evaluation.

Included studies

Three randomised controlled trials, including 169 participants, met our inclusion criteria and were included in this review (Alvim 2005; El-Hazmi 1998; Mikati 1983). Two trials had multiple publications (Alvim 2005; El-Hazmi 1998). For the El Hazimi trial we chose to use the most recent published report of this trial in our review as it

provided more complete data and trial details. The other references to this trial are listed as secondary references under the primary reference (El-Hazmi 1998). For the Avim trial we used the initial publication in 2005 as this was the primary reference; the 2009 reference was a supplementary publication (Alvim 2005).

Alvim trial

The Alvim trial was a double-blind, randomised, placebo-controlled cross-over trial conducted in Brazil from September 1998 to December 1999 (Alvim 2005). A pilot study was carried out to determine the appropriate sample size and to test "the questionnaires and pain scores". The authors confirmed that this was an observational study and did not include any intervention. Several of the participants in the pilot study were also included in the clinical trial but all pain scores recorded during the pilot study were discarded at the start of the clinical trial.

Participants

A total of 80 participants were enrolled, but 7 were considered non-compliant during the early part of the trial and were excluded from the analysis leaving 73 children (33 males) aged 5 to 20 years (median 12.1). All were suffering from sickle cell disease and were diagnosed as, Hb SS 42 (57.5%), HbSC 26 (35.5%), and 5 (7%) Hb Sß thalassaemia. The authors indicated that the genotype of participants enrolled in the trial was confirmed by haemoglobin electrophoresis but the diagnostic details were not reported.

The trial authors specified as their inclusion criteria for this trial that all participants should have experienced moderate to severe painful crises defined as painful episodes of variable intensity and duration occurring in the limbs, vertebral spine and thorax or abdomen and which had been recognised by patients and carers as the typical pain attributable to the disease. Other painful events, i.e. priapism, avascular bone necrosis, osteomyelitis and acute chest syndrome were excluded. Additional exclusion criteria were: (1) renal, hepatic, cardiac or coagulation disorders secondary or not, to sickle cell disease; (2) regular blood transfusion, whatever the indication; (3) use of hydroxyurea; (4) age above 20 or below 5 years; (5) cognitive dysfunction that would hinder the reporting of pain
Fifty of the participants had received one or more transfusions before the start of the trial, 5 (6.3%) had undergone splenectomy and a further five cholecystectomy. Acute splenic sequestration had occurred in 12 (15%), osteomyelitis in 11 (13.8%), aplastic crisis in one, and avascular necrosis of the femoral head in 4 (5%) participants.

Interventions

Randomisation was to oral piracetam 4.8 g/m^2/day every six hours or placebo. Piracetam was administered to half the participants and placebo to the other half for six months and these were crossed over for the following six months. The trial included a four-week washout period, at cross-over, consisting of a tapering off for two weeks followed by an additional two weeks without any medication. Compliance with the trial regimen was reinforced through regular home calls, evaluated by a pill count and monitored by regular urinary assay of piracetam levels.

Outcomes

Participants or their carers, or both, completed weekly questionnaires which assessed the clinical status and symptoms of the participants. The questionnaires recorded aspects of general well-being, the frequency length and type of painful crises, pain intensity and its site, the effect of the disease on school or work attendance, as well as sleeping, eating and other daily activities, the type of analgesia used and any need for ambulatory medical assistance or hospital admission. Pain intensity was assessed on a three-point ordinal scale, (0 = no pain, 1 = bearable pain, 2 = unbearable pain), from which monthly pain scores were calculated. In addition clinicians completed monthly questionnaires, which recorded and characterised the painful crises and their treatment, during the course of the trial.

El-Hazimi trial

The El-Hazimi trial was a multicentre double-blind, randomised, parallel group trial conducted from 1992 to 1994 in 13 centres in Saudi Arabia (El-Hazmi 1998).

Participants

A total of 101 children aged three to 12 years who had sickle cell disease (SCD and Hb S/ß thalassemia) were enrolled in the trial. The trial authors indicated that 16 dropped out at an early stage and that only 87 completed the trial. We have tried to contact the trial authors by electronic mail on several occasions to seek clarification of the discrepancy in the numbers of participants who were enrolled, those who dropped out and those who completed the trial but so far have received no response. The majority of the participants (79) were from the Western region of Saudi Arabia, where the Benin haplotype is prevalent, whilst the remainder (eight) were from the Eastern region, and had the Saudi Indian haplotype.

Baseline data of sex, age, height, weight, number of crises, number of blood transfusions and hospitalisations, the 'Severity index' (El-Hazmi 1990) and the 'Gini score' (Gini 1987) were recorded at enrolment. The bibliographical reference quoted by the authors, to this 'score', does not provide any additional information and refers to an index of red cell deformability (IRCD) which does not appear to be directly related to the 'Gini score'.

The trial authors indicated that at enrolment the diagnosis and classification of participants as SS or Sß0 thalassemia was based on the results of haemoglobin electrophoresis, red cell indices, HbA2 and Hb F levels but did not provide the values for these individual genotypes.

The inclusion criteria for the trial specified that at entry the participants should have a disease severity greater than six as measured on the 'Severity index' (El-Hazmi 1992). This index, which was developed by the authors and does not appear to be internationally recognised, was designed to be used as a quantitative measure of the severity of sickle cell disease based on a combination of hematological, biochemical and clinical parameters consisting of six reversible and seven chronic complications which occur in sickle cell disease.

Interventions

The participants were randomised to receive oral piracetam (48) or placebo (39) in a dose of 160 mg/kg/day but during any crisis they were admitted to hospital and received 300 mg/kg/day of piracetam or placebo by intravenous infusion. On discharge the participants were returned to their standard oral regimen. The report did not record if any tests of regimen compliance were carried out during the course of the trial.

Outcomes

Clinical assessments were carried out routinely every 8 to 12 weeks during the trial period and included the recording of routine hematological and biochemical parameters, the point scores of which were added up to provide an annual 'Severity index'. During any admissions participants were assessed clinically and blood samples were taken for evaluation of hematological parameters. At the conclusion of the trial, all participants living in Riyadh were followed up every three months for the whole of the following year.

Outcomes assessments for this trial were largely based on the 'Severity index' which consisted of a checklist of parameters which were described as possible reversible and chronic complications of sickle cell disease. Several of the items in this index were poorly defined and based on unsubstantiated assumptions of clinical status in sickle cell disease. Reversible complications included among others the number of transfusions received by participants but as clinical decisions for transfusion may be based on arbitrary criteria and not infrequently on the preferences of the individual clinician, this item might be considered an unreliable indicator of severity of sickle cell disease. Other items which were listed as chronic complications included cardiomyopathy, papillary necrosis and gallstones but were also equally ill-defined and the authors did not clarify if any of these complications were detected as a result of symptoms or through routine screening, nor how they would be able to detect impotence in children under 12 years old. This index was developed by the authors as a quantitative measure of the severity of the sickle cell disease which they state that they found to be a useful measure to assess the beneficial effect or otherwise of the drug. However, the absence of a scaling capability of any of the individual items in this index may also reflect its poor sensitivity and competency to discriminate the degree in severity of individual pain crises. The authors also indicated that they used the 'Gini score' for evaluation of disease severity and whilst including data for both intervention groups in their report they did not provide any information on how this score was calculated or how the assessments were made.

Mikati trial

The Mikati trial consisted of a double-blind cross-over clinical trial and an 'experimental' study both of which were conducted in Lebanon between 1981 and 1982 (Mikati 1983).

Participants

Thirteen children aged 4 to 15 years, who were diagnosed with sickle cell disease by haemoglobin electrophoresis (Goldberg modification of the starch gel electrophoresis) (Goldberg 1958) entered the trial, but four dropped out because of irregular follow up which left nine children (five female, four male) who completed the trial.

Interventions

In the clinical trial the participants received either piracetam I0 mg/kg/day orally in four daily doses, or placebo consisting of identical capsules which contained 300 mg lactose. The capsules were "chosen randomly" and the participants took them for five months, and then the interventions were crossed-over for a similar period but no information about a washout period or any further trial details were provided by the authors. The 'experimental' study included in this report was an observational study which assessed the effects of piracetam on erythrocyte survival, in a separate group of participants and is therefore not included in this review.

Outcomes

The stated primary outcome in this trial was the frequency of painful crises but the trial authors did not clarify how these were diagnosed or assessed.

Excluded studies

We excluded five studies: a report of a non-controlled study (De Araujo 1977); an open study (De Melo 1976); an in vitro study (Franklin 1980); a two part, in vitro and in vivo observational study (Gini 1987); and an observational study (Sonnet 1985).

Risk of bias in included studies

Please refer to the Additional tables section of the review for information on the methodological quality of the included studies (Table 1).

Allocation

Alvim trial

The participants were randomly assigned to the intervention (oral piracetam) and control (placebo) groups; however, the method of randomisation was not specified in the report (Alvim 2005). We wrote to the investigators who confirmed that randomization was achieved through the use of computer-generated random numbers and only one investigator, who was not involved with clinical care, was aware of the code to the allocation sequence. Randomization was graded as (A) adequate, but because not all of the investigators were blinded to the allocation sequence this criterion was graded as inadequate (C).

El-Hazmi trial

The trial authors reported that participants received piracetam or placebo and that neither the participant nor clinicians were aware what the participant was receiving (El-Hazmi 1998). The active intervention (oral piracetam and intravenous infusion) and placebo (oral and intravenous infusion) were provided in coded boxes by the UCB Company; however, the method of randomisation of participants to active intervention or placebo was not specified and therefore this criterion was graded as unclear (B). The code to the allocation sequence was retained in the Head Office of the UCB Company in Brussels and therefore it was considered that adequate attempts had been made to conceal the allocation sequence from the trial authors. The deciphering of the allocation code only occurred at the end of the trial period and therefore this criterion was graded as adequate (A).

Mikati trial

The trial authors reported that the interventions were 'randomly chosen' rather than individuals being randomised to intervention or control, they also failed to provide any information about the methods use to conceal the allocation sequence from either participants or trial authors and therefore both of these criteria were graded as inadequate (C) (Mikati 1983).

Blinding

Alvim trial

The participants and researchers were blinded to intervention and control and the principal outcomes were self-assessed therefore this criterion was graded as 'yes'.

El-Hazmi trial

The participants and investigators were blinded to intervention and control and therefore this criterion was graded as 'yes'. However, the trial authors did not clarify if the outcomes assessors were blinded to the interventions received by the participants and thus this criterion was graded as 'unclear'.

Mikati trial

The capsules of active intervention and placebo were indistinguishable from each other and thus the investigators and participants were blinded to the interventions until after the completion of the trial and the analysis of its data, consequently this criterion was graded as 'yes'.

Incomplete outcome data

Alvim trial

Of the 80 participants enrolled in this clinical trial seven were considered non compliant, six of whom the authors confirmed did not attend scheduled clinic visits over the first two months of the trial. The remaining participant was excluded after seven months of difficult follow up and failure to attend for clinic visits. The early dropouts were not included in the analysis, and all those who completed the trial were included in the final analysis and therefore this criterion was graded as yes (A)

The trial authors confirmed that although the active medication (piracetam) was donated by Biossintetica Laboratory and the placebo was manufactured by Ezequiel Dias Foundation, Health Department, Minas Gerais, neither of these two institutions had any active participation in the trial. Financial support for the trial was provided by FAPEMIG (State of Minas Gerais Research Foundation) and CNPq (Brazilian National Research Council) both of which are public institutions.

El-Hazmi trial

A total of 101 children aged three to 12 years who had sickle cell disease (SCD and Hb S/ß thalassemia) were enrolled in the trial and the trial authors indicated that 16 dropped out at an early stage and that only 87 completed the trial. The report of this trial provided a clear description of losses and withdrawals to the trial and thus this criterion was graded as yes (A); however, their data analyses did not follow the 'intention-to-treat' principle.

The authors indicated that the drug and placebo, in addition to some unspecified help, were provided by UCB Company during the course of the trial (El-Hazmi 1998).

Over and above the uncertainty of the 'Severity index' as a reliable and valid measure of severity in sickle cell disease crises, there are additional concerns about the methodological quality of this trial. These include the absence of a clear definition or criteria of a severe painful crisis, a major outcome in this trial, and no indication of the methods used to achieve standardisation of outcomes assessment between the trial authors in the 13 different centres.

Mikati trial

All losses to the trial were accounted for therefore this criterion was graded as 'yes' (A), and the analysis of participants was to the treatment they were allocated.

This trial included a 'clinical' and an 'experimental' study, but the reporting of trial details and data from these studies was scanty, unclear and somewhat confusing (Mikati 1983). No sample size or power calculation was performed for what was essentially a small sample study. The trial authors did not clarify the genotype of each participant at enrolment, and only stated that sickle cell anemia was confirmed by haemoglobin electrophoresis but did not include any diagnostic details. The duration of intervention in each trial arm was not clearly stated nor was there any indication of a washout period. The primary outcome sought in this trial was the frequency of painful crisis but the trial authors did not provide a definition or clarify their criteria for a painful crisis, nor how the severity of each crisis was to be assessed.

Effects of interventions

A limited amount of data addressing some of the primary, in addition to some of the secondary outcomes, was provided by all three of the included trials (Alvim 2005; El-Hazmi 1998; Mikati 1983). These data, as discussed in 'Description of studies' and 'Risk of bias in included studies', are based on unvalidated assumptions used in the evaluation of outcomes, therefore we have not entered these data into the RevMan analyses but present the reported data within 'Additional tables' where appropriate (Table 2; Table 3).

Primary outcomes

1. Number of painful sickle cell disease crises

The average number of pain crises per participant per month reported in the Mikati trial was 0.89 with piracetam and 1.85 with placebo ($P < 0.05$) (Mikati 1983). The severity of these crises was reportedly much less with active intervention than placebo but no data were available to confirm these results.

The authors in the El-Hazmi trial reported data for this outcome (El-Hazmi 1998). *See* 'Additional tables' (Table 2).
The Alvim trial did not provide any separate data for the number of sickle cell crises or severity of pain but included these in a monthly global pain score which was calculated by combining data on the length and intensity of each episode during the trial (Alvim 2005). However, it was not possible to unravel these data to provide information on the primary outcomes specified for this review.

2. Mortality

None of the included trials provided data on mortality.

Secondary outcomes

1. Pain: intensity and duration

Only the Alvim trial assessed pain severity but the data were included in a monthly pain score and not available as separate scores (Alvim 2005).

2. Requirement for opiate treatment

None of the included trials provided any data on requirement for opiate requirement.

3. Serious complications

None of the included trials provided data on serious complications.

4. Red cell dehydration

None of the included trials provided data on red cell dehydration.

5. Number of other sickle-related events

The only event reported was of one child with a deep ulcer on her cheek which was alleged to have improved dramatically during the course of the trial (El-Hazmi 1998).

6. Quality of life

Only generalised and subjective improvements were reported, none of which were supported by any validated instruments.

7. Hospitalisation

In the Alvim trial, the number of days of hospitalisation ranged from 0 to 42 (median 1) and in 93.5% a painful crisis was involved but there was no significant difference between the piracetam and placebo periods for the number of days of hospitalisation (P = 0.87).

Data for the number of hospitalisations were reported in the El-Hazimi trial (El-Hazmi 1998). *See* 'Additional tables' (Table 3).

8. Satisfaction with medication

The authors in the Alvim trial reported that nearly all participants and their relatives indicated their satisfaction with the clinical course of the trial, but no details were provided about how this was evaluated or the type of questionnaire or assessment tool that was employed (Alvim 2005). El-Hazmi indicated that parents of the participants insisted on continuation of therapy, thereby showing their satisfaction but provided no details as to how this satisfaction had been assessed (El-Hazmi 1998).

Adverse effects

No clinical or laboratory evidence of toxicity to piracetam was reported in either the Alvim or the El-Hazmi trial (Alvim 2005; El-Hazmi 1998). The authors in the Mikati trial reported that one participant experienced dizziness with the drug (Mikati 1983).

DISCUSSION

The lack of reliable evidence for the effectiveness of piracetam is illustrated by the paucity of trials retrieved for this review. However, the wide divergence of reported results in the included trials and the apparent lack of popularity of this drug by clinicians over the past 20 years would appear to suggest and possibly confirm some of the uncertainty in the effectiveness of this medication in preventing painful sickle cell crises.

The episodic nature of sickle cell crisis pain, with its propensity to affect multiple sites, difficulties in conducting pain prevention studies in sickle cell disease, the relatively subjective nature of observer-rated pain intensity, and the absence of a drug which meets a 'gold standard' that can be compared to either piracetam or any other known compounds with established effectiveness in preventing or reducing pain in sickle cell crises by treating the sickling process, sets challenges for any future trials of effectiveness of this specific medication.

We will continue to run searches on a two-yearly cycle to identify any potentially relevant trials; however, we do not plan to update other sections of this review until new trials are published.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the routine use of this medication for reducing the incidence of painful sickle cell disease crises.

Implications for research

Future research should aim to provide evidence for people to make informed decisions about whether piracetam is effective and therefore any further randomised controlled trials should use larger samples, longer intervention and washout periods if appropriate, include a lengthier follow-up period and be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement.

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Original review

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2015 update

The authors would like to thank Ghazi Tadmouri and Ahmed Omran for their contribution to the original version of this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alvim 2005

Study characteristics	
Methods	Double-blind, randomised, placebo-controlled cross-over design. Group 1: active intervention. Group 2: placebo for 6 months. Washout period, tapering for 2 weeks and no medication for a further 2 weeks followed by cross-over.
Participants	Age 5 - 20 years (median 12.1), 33 males (45.2%) and 40 females (54.8%). 42(57.5%) were Hb SS, 26 (35.5%) Hb SC and 5 (7%) were Hb Sß thalassemia.
Interventions	Piracetam orally 4.8 g/m^2/day or placebo 4 times per day
Outcomes	Clinical status self assessed weekly by questionnaire: 1. general child well-being; 2. frequency, length and description of the painful crises; 3. intensity of the painful crises recorded using an analog-visual scale; 4. pain pinpointing recorded in a body diagram; 5. identification of whether the painful crisis was characteristic of the disease;

Alvim 2005 *(Continued)*

	6. school or work attendance; 7. impossibility of sleeping, eating, walking, playing, doing outdoor activities, studying, watching television; 8. type of analgesia used and the domiciliary activities for pain relief; 9. need for ambulatory medical assistance; 10. need for hospitalization and treatment. Monthly physician completed questionnaire recording and characterising the painful crises and treatment. End of study, separate patient and relatives questionnaire: 1. motivation for study enrolment; 2. impression of the outcome of the disease; 3. possible pain-inducing factors; 4. impact of the disease on their lives.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Inadequate.

El-Hazmi 1998

Study characteristics	
Methods	Double-blind, randomised, placebo-controlled parallel trial
Participants	Age: two groups; 3 - 6 years and 7 - 12 years, 50 males and 37 females. 79 were Hb SS and 8 were Hb Sß thalassemia
Interventions	48 received piracetam orally 160 mg/kg/day during follow up and 39 matched placebo. During crises intravenous infusion of 300mg piracetam or placebo /kg/day
Outcomes	Severity Index (SI) a composite measure of biochemical investigations, signs symptoms and other markers: Hb level, reticulocyte cytopenia, bilirubin level, LDH, number of severe painful crises/year, stroke/deep venous thrombosis, interstitial lung disease, cardiomyopathy, gallstones, papillary necrosis, aseptic necrosis, impotence, short stature.
Notes	This trial included the use of a 'rescue medication' of piracetam administered intravenously.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate.

Mikati 1983

Study characteristics

Mikati 1983 *(Continued)*

Methods	Double-blind, cross-over clinical trial.
Participants	Ages 4 - 15 years, 5 females and 4 males (13 were enrolled 4 dropped out)..
Interventions	Piracetam 80 mg/kg/day orally divided into four daily doses or placebo orally as four daily doses of capsules consisting of 300 mg lactose, for 5 months and then crossed over for a similar period.
Outcomes	The average number of pain crises per month.
Notes	Trial details were unclear and incomplete. The criteria for pain crises were not specified. No details on how pain was assessed were reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Inadequate.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
De Araujo 1977	Letter/report of a comparative non-controlled study.
De Melo 1976	Observational open study.
Franklin 1980	Letter/report of an in vitro study.
Gini 1987	*In vitro* and *in vivo* study. The *in vivo* part was an observational study only.
Sonnet 1985	Observational study.

ADDITIONAL TABLES

Table 1. Quality of included studies

Study ID	Randomization	Concealment	Blinding	Intention-to-treat	Attrition
Alvim 2005	Clear (confirmed by email correspondence with authors)	Inadequate	To intervention: yes Outcomes assessment: yes	Yes, all participants included in the analysis	All dropouts were accounted for, 6 occurred at the beginning of the trial and 1 after 7 months. They were not included in the analysis
El-Hazmi 1998	Unclear	Adequate	To intervention: yes Outcomes assessment: unclear	No, only 87 out of 101 participants were analysed	Dropouts occurred at an early stage of the trial but the stated number of participants completing the trial does not agree with the numbers enrolled minus the dropouts

Table 1. Quality of included studies *(Continued)*

Mikati 1983	Inadequate	Unclear	To intervention: yes Outcomes assessment: unclear	Yes, all participants who completed the study were analysed	Dropouts constituted > 25% of the total

Table 2. Number of sickle cell crises (El-Hazmi 1998)

Time points	3 - 6 years (piracetam)	3 - 6 years (placebo)	7 - 12 years (piracetam)	7 - 12 years (placebo)
Baseline Mean (SD)	4.6 (3.7)	3.0 (1.1)	5.1 (3.6)	4.2 (1.5)
After treatment	2.2 (1.9)	4.3 (2.9)	2.3 (1.6)	4.5 (3.3)

Table 3. Number of hospitalisations (El-Hazmi 1998)

Time points	3 - 6 years (piracetam)	3 - 6 years (placebo)	7 - 12 years (piracetam)	7 - 12 years (placebo)
Baseline Mean (SD)	3.5 (3.0)	3.4 (3.0)	4.3 (3.4)	2.9 (2.1)
After treatment	1.9 (2.6)	2.2 (1.9)	2.4 (2.5)	1.5 (2.0)

WHAT'S NEW

Date	Event	Description
8 April 2021	Review declared as stable	This area of research is no longer active. Date of most recent search: 21 September 2015.

HISTORY

Protocol first published: Issue 3, 2006
Review first published: Issue 2, 2007

Date	Event	Description
19 October 2015	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Haemoglobinopathies Trials Register did not identify any potentially relevant references for inclusion in any section of the review. The 'Plain language summary' has been updated in line with the most recent Cochrane guidelines.
19 October 2015	New citation required but conclusions have not changed	For this update, we have not identified any further trials. We will continue to run searches to identify any potentially relevant tri-

Date	Event	Description
		als; however, we do not plan to update other sections of the review until new trials are published.
4 February 2015	Amended	Minor amendments made to the 'Abstract' and 'Plain language summary' to accurately reflect that this review is no longer being updated.
9 March 2011	Review declared as stable	We do not plan to update this review until new trials are published, although we will search the Group's Haemoglobinopathies Trials Register on a two-yearly cycle.
9 March 2011	New search has been performed	No new trials were identified in the 2011 search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register.
29 July 2010	New search has been performed	The search of the group's Haemoglobinopathies Trials Register identified a further reference to one of the included studies (Alvim 2005). However, no additional data were eligible for inclusion in the review.
7 November 2008	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identify any trials potentially eligible for inclusion.
1 October 2008	Amended	Converted to new review format.
1 February 2008	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identify any new references for consideration for inclusion in this review.
1 February 2008	Amended	The previous 'Synopsis' has been replaced with a new 'Plain language summary' in line with guidance from The Cochrane Collaboration.
1 February 2007	New search has been performed	Some post hoc changes have been made in 'Types of outcome measures': 1. 'Mortality' has been moved to 'Secondary outcomes' from 'Primary outcomes'. 2. 'Number of sickle cell disease crises' has been amended to "Number of painful sickle cell disease crises". 3. 'Pain' has been moved to 'Primary outcomes' from 'Secondary outcomes'. 4. 'The requirement for opiate treatment ' has been moved to 'Primary outcomes' from 'Secondary outcomes'. Also, "during hospitalisation, Accident & Emergency Department visits or on discharge to home" has been added to this outcome.

CONTRIBUTIONS OF AUTHORS

For the original review

Amani Al Hajeri conceived the idea for the review and is the guarantor for the review.

Amani Al Hajeri and Zbys Fedorowicz were responsible for:

- designing the review;
- co-ordinating the review;

- performing previous work that was the foundation of this current study;
- organising retrieval of papers;
- writing to authors of papers for additional information;
- providing additional data about papers;
- extracting data from the papers, entering data into RevMan and analysing the data.

Ghazi Tadmouri and Ahmed Omran screened the retrieved papers against inclusion criteria.

All authors appraised the methodological quality of papers and were jointly responsible for interpretation of the data and writing the review.

For the 2015 update

Amani Al Hajeri and Zbys Fedorowicz made minor changes throughout the review.

DECLARATIONS OF INTEREST

Amani Al Hajeri: none known.

Zbys Fedorowicz: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK

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INDEX TERMS

Medical Subject Headings (MeSH)

Anemia, Sickle Cell [complications] [*drug therapy]; Antisickling Agents [*therapeutic use]; Pain [*drug therapy]; Piracetam [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Child, Preschool; Humans